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METASTATIC NEUROENDOCRINE CARCINOMA OF THE PROSTATE PRESENTING WITH DISSEMINATED INTRAVASCULAR COAGULATION: IMPORTANT CLUES FROM A PERIPHERAL BLOOD SMEAR EXAMINATION

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ABSTRACT: Prostate cancer commonly metastasizes to bone, liver and lung but bone marrow (BM) involvement is rare. Most common coagulopathy in prostate cancer is Disseminated Intravascular Coagulation (DIC) with 0.4% to 1.65% of patients presenting with subclinical DIC. The Leucoerythroblastic reaction on the peripheral blood smear in this case prompted for a Bone Marrow(BM) examination leading us to the diagnosis in conjunction with the clinical and radiological findings. We report a case of Large Cell Neuroendocrine Carcinoma (LCNEC) of prostate with first presentation as bone with bone marrow metastasis and chronic DIC. Our case confirms the fact that such presentation is rare with an aggressive clinical course and poor prognosis. It also highlights the possibility of coagulopathy in such cases. The fact that DIC in LCNEC of prostate has not yet been reported in the literature makes our case report unique.

KEY WORDS: Leucoerythroblastic reaction, Bone Marrow, Disseminated Intravascular coagulation, Large Cell Neuroendocrine Carcinoma, Prostate Cancer

INTRODUCTION: Peripheral blood smear examination in unexplained cytopenias can be of utmost importance as Microangiopathic hemolytic anaemia (MAHA), Leucoerythroblastic reaction (LEB) are pertinent pointers for Bone marrow aspirate and biopsy to rule out infiltrative disorders of BM especially in the context of diagnosis of unsuspected non-haematologic malignancy.[6] This can lead to diagnosis of solid organ tumours from the bone marrow which is unusual. Though coagulopathy is known in non-haematological malignancies including Prostatic carcinomas but subclinical Disseminated Intravascular Coagulation(DIC) and Bone Marrow involvement as the presenting signs in metastatic prostatic carcinomas is rare.[1,4] There are very few case reports in the literature[1,3,6,7]. Among less common variants of prostate cancer particularly with neuroendocrine differentiation, DIC has not been well documented. One such rare entity is Large Cell Neuroendocrine Carcinoma(LCNEC) of

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prostate. So far the clinicopathologic features of this rare manifestation of advanced prostate cancer have been summarized in only 7 cases[9]. BM involvement and DIC in this rare variant of neuroendocrine carcinoma of prostate has not been reported in the literature and in such cases are poor prognostic factors. Treatment with Androgen Deprivation Therapy(ADT) is not effective. Therefore, chemotherapy should be initiated in the beginning is debateable as the prognosis is still poor in these cases.

CASE REPORT: A 54 year old male was referred to a Referral Tertiary Oncology Center in India with history of fever, fatigue, cough, back pain and pancytopenia (Hb:7.2 g/dl, ANC:<1500cells/cumm, PC:75,000/cumm) since 1 month. His peripheral blood smear (PBS) examination showed Leucoerythroblastic reaction (Blasts-03%,Myelo/metamyelocytes-08%,Polymorphs:51%,Lymphocytes:32%,Monocytes:5%,Eosinophils:1%,6nRBCs/100WBCs)

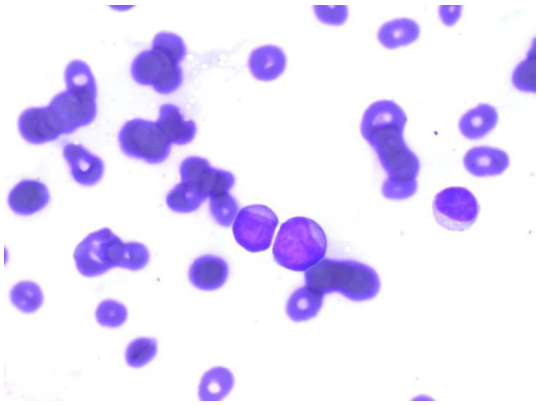

Figure 1A: PBS (Romanowsky stain,40X): Blasts

[Figure 1A and B] raising the suspicion of BM metastasis and prompted for a BM examination in our patient. On clinical examination, he did not have any lymphadenopathy and organomegaly. On digital rectal examination (DRE) he had an enlarged hard and fixed prostate but there was no rectal mass. So his serum PSA was done which was found to be 11.47ng/ml(Reference range:0-4ng/mL). His coagulation profile was also deranged.

PT:83.8sec (11.1-14.5seconds), INR:7.55,D-dimer:8424.83ng/ml, Reference range:<500ng/ml) though his APTT(25.2

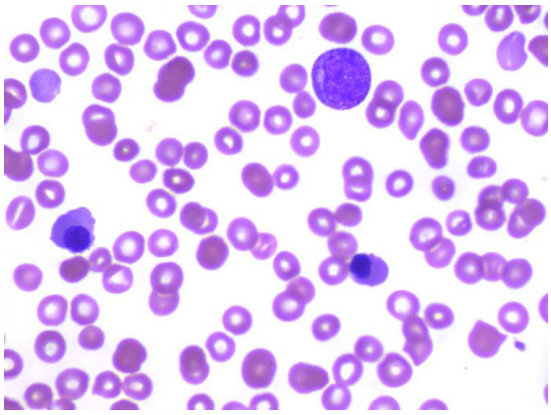

Figure 1B: PBS (Romanowsky stain,40X): Left shift and nRBCs

seconds, Reference range:25.2-31.2 seconds) and fibrinogen levels were normal(261.5 mg/dl, Reference range: 150-450mg/dl). On ½ patient plasma and ½ control plasma mixing study, there was complete and immediate correction and the values obtained were PT:12 sec,INR:1.08. Other Laboratory investigations revealed an elevated Lactate Dehydrogenase (LDH:8111U/L,Reference range:313-618U/L) and Alkaline Phosphatase (ALP:1075 U/L,Reference Range:38-126U/L). Subsequently, he underwent BM biopsy and aspiration procedures. His BM aspirate smears exhibited predominantly cohesive clusters and discrete malignant epithelial cells. Glandular formations and rossettes of tumour cells were seen. These malignant epithelial cells were large with high N/C ratio and nuclear pleomorphism. Hematopoietic elements were markedly depleted. Megakaryocytes were absent.

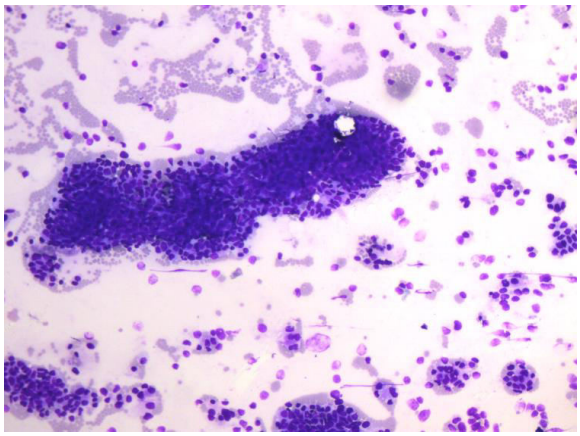

Figure 2 A : BM aspirate smear (Romanowsky stain,4X)

[Figure 2A,B]. Decalcified sections of BM trephine biopsy were hypercellular and were entirely replaced by sheets and cohesive clusters/groups of malignant epithelial cells separated by fibrous septa. These tumour cells were large,polygonal with round nucleus, vesicular chromatin and prominent nucleolus with moderate amounts of Vacuolated/clear cytoplasm.

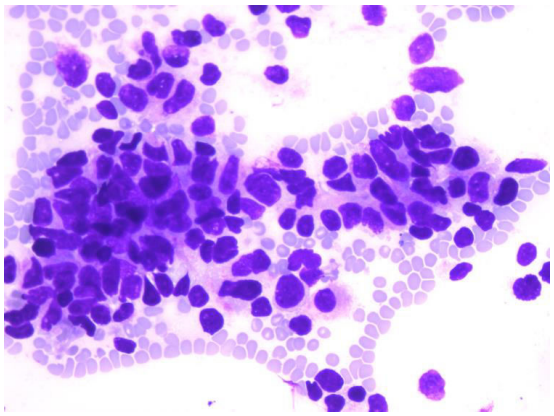

Figure 2B: BM aspirate smear (Romanowsky stain,40X)

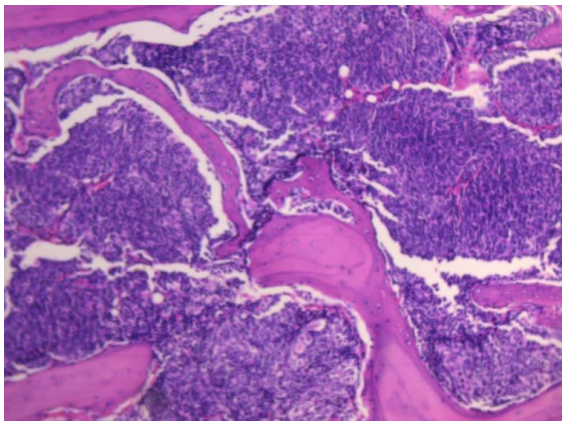

Figure 3A: BM biopsy (H and E,10X)

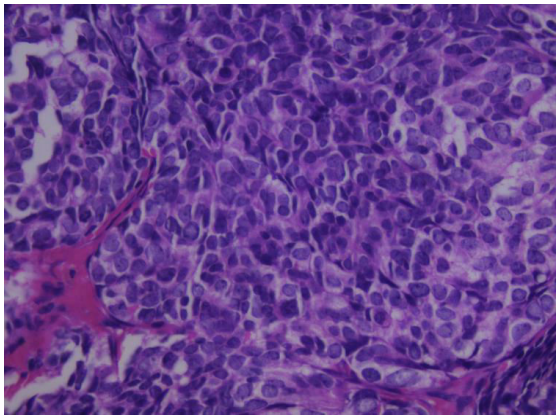

Figure 3B: BM biopsy (H and E,40X)

[Figure 3A,B]. BM reticulin fibrosis was increased [Figure 4]. Pancytokeratin and

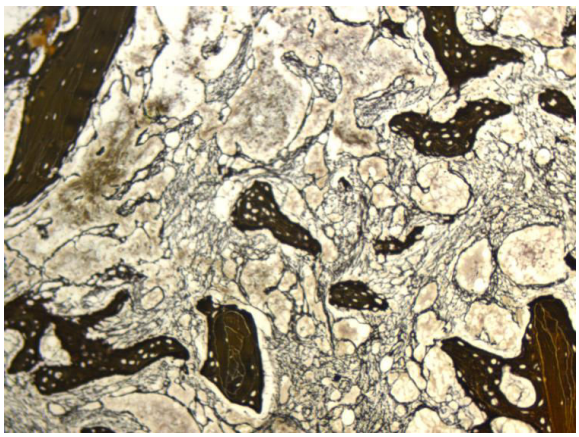

Figure 4 : Reticulin stain,10X

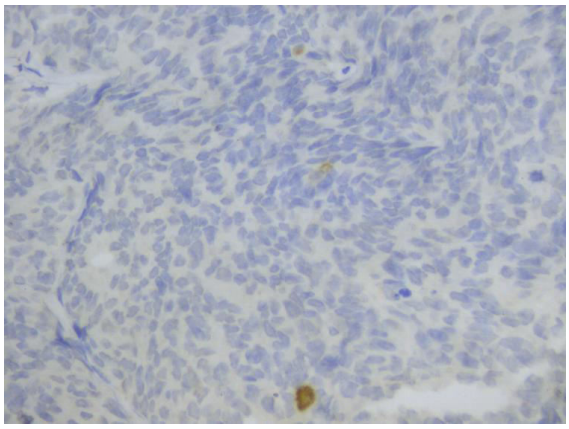

Figure 5A: PSA, 40X

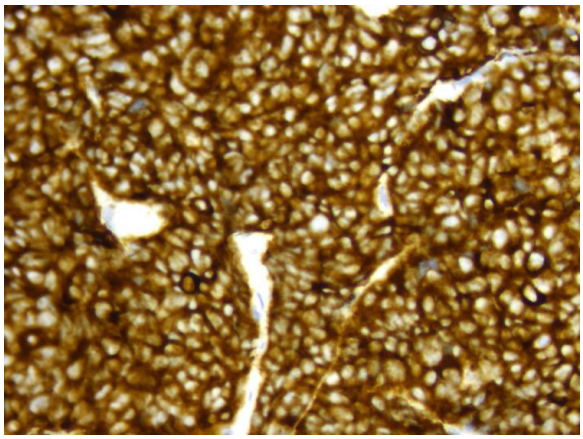

Figure 5B: Synaptophysin,40X

Prostate Specific Antigen(PSA)[Figure 5A]immunostainings done on BM biopsy were negative on tumour cells. Since PanCK was negative, CK8/18 was done along with CDX2, TTF1 and neuroendocrine markers

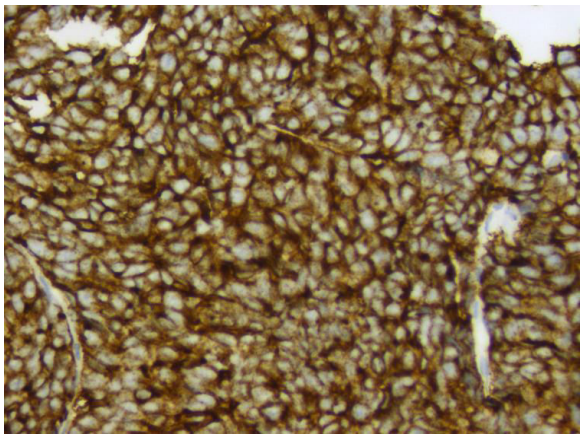

Figure 5C: Chromogranin A,40X

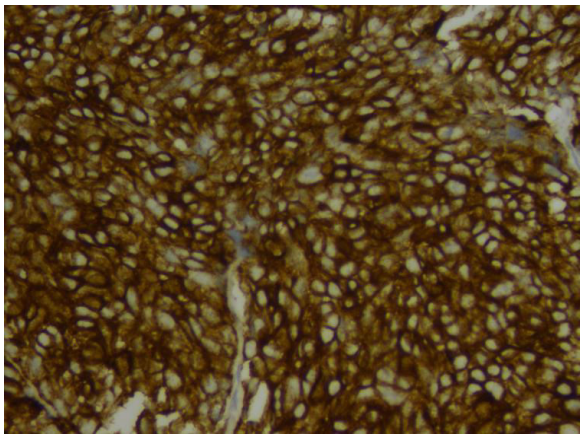

Figure 5D: CK8/18,40X

Chromogranin A, Synaptophysin and AMACR. CK8/18 is positive in tumours with neuroendocrine differentiation. CDX2 was done to rule out metastasis from colonic carcinomas whereas TTF1 excludes metastasis from lung carcinomas. AMACR is particularly positive in large cell neuroendocrine carcinomas. Since he complained of back pain, X-ray of lumbar-spine(LS) and pelvis was done which showed sclerotic secondaries. His Computed Tomography(CT) scan of abdomen showed hepatosplenomegaly and prostatomegaly. Magnetic Resonance Imaging (MRI) of pelvis was done and showed focal lesion involving apex and midgland of prostate with altered marrow signals in pelvic bones and lumbar vertebra [Figure 6A] and pelvic

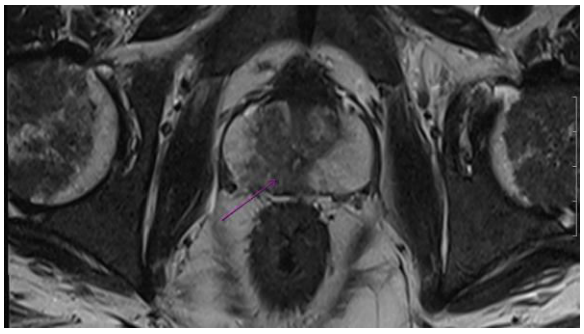

Figure 6A: MRI Pelvis:- T2 weighted axial image (arrow)

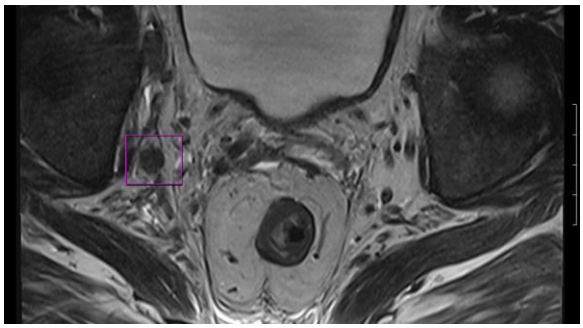

Figure 6B: MRI Pelvis:- T2 weighted axial image (square box)

lymphadenopathy [Figure 6B]. Whole body bone scan study showed disseminated skeletal metastasis. Positron Emission Tomography Computed Tomography (PET CT) showed multiple tiny peripherally placed soft tissue nodules in both lungs, possibly metastatic.

The immunostainings done on BM biopsy were negative for PSA/ CK/ CDX2/ TTF-1. The tumour cells were strongly and diffusely positive for the neuroendocrine markers i.e. synaptophysin and chromogranin A [Figures 5B,C]. CK8/18 (cam 5.2)[Figure 5D] was also strongly and diffusely positive in these tumour cells. AMACR (alpha methylacyl CoA racemase) immunostain was focally positive. So, BM showed metastatic carcinoma of neuroendocrine differentiation, most likely from prostate. Prostatic biopsy was planned but could not be done due to consistently deranged PT/INR(83.8 sec/7.55) and very high D-dimer (8434.83 ng/ml) but with normal APTT (25.2 sec) and fibrinogen levels (261.5mg/dl). His platelet counts were less than 60,000/cumm initially but slightly increased thereafter and hovered around 60,000-1,00,000/cumm . He had no evidence of bleeding from any site.

Based on the above clinical, radiological and histopathological profile a final diagnosis of Metastatic Large cell Neuroendocrine Carcinoma of Prostate with bone and bone marrow involvement with chronic compensated DIC was made. He was treated with androgen deprivation therapy (ADT) in the form of GnRH analogues. He was not considered for chemotherapy in view of his poor performance status. His coagulation profile remained stable throughout the therapy except PT/INR and D-dimer which continued to be elevated. His platelet count gradually recovered to around 1.2 lacs/cumm and patient didn't require any Fresh Frozen Plasma (FFP) and or platelet transfusions after ADT. After 5 months of the therapy he developed respiratory infections and succumbed to death.

DISCUSSION:

The incidence of DIC in metastatic tumours is 10%-15%.[1] and incidence in prostate cancer is close to 25%[2] Ruffion reported 13 to 30% incidence of DIC but clinical signs of DIC were actually found in only 0.4 to 1.65% of patients.[3] In prostate cancer, the incidence of DIC is dependent on the tumour stage and it is enhanced in metastatic hormone-refractory disease[4]. The different procoagulant substances such as tissue factor (TF) expressed at the surface of tumour cells and a cancer procoagulant (CP) may be involved in the pathogenesis of DIC[4] .Some authors have also demonstrated that prostate tumour cells are rich in thromboplastin[5] which is another contributing factor causing DIC. BM metastasis commonly arise from lung, breasts and prostate cancers[6]. Microangiopathic hemolytic anaemia

(MAHA), Leucoerythroblastic reaction (LEB) and unexplained cytopenias are strong indicators of the necessity of BM examination[6]. Our patient also had pancytopenias and LEB. Although DIC is the most frequent coagulation disorder in patients with prostate cancer, DIC as a first manifestation with BM involvement is rare with only few published case reports[1,7]. Approximately 13% of patients of carcinoma prostate develop some form of chronic DIC syndrome which usually presents as low grade bleeding tendency with or without venous thrombosis[8]. Fibrinogen concentration is low in only 50% of the patients and is usually associated with severe cases of DIC[4] while in our case it was normal.

The immunoprofile of our patient was consistent with LCNEC of prostate. AMACR is particularly positive in this rare variant of neuroendocrine carcinomas of prostate[9]. Prostatic LCNEC is characterized by low PSA levels, negative PSA immunostain, aggressive clinical course, predilection for bony spread and widespread metastasis[9] and all of these were present in our case. Primary neuroendocrine tumours arising from lung and colon were excluded by CDX2 and TTF1 negativity respectively in our case[13,14]. Prostatic biopsy can be hazardous in the presence of DIC and can lead to death as there is a risk of systemic release of coagulopathic mediators[10] which is the reason we didn't try the prostatic biopsy.

Our patient had subclinical/chronic DIC as his APTT and fibrinogen were normal[11] and his platelet count recovered gradually. In chronic, compensated DIC the liver can offset the consumption of clotting factors and the bone marrow maintains an adequate platelet count[12] which also happened in our patient. LCNEC is not a hormone sensitive tumour and primary treatment of LCNEC is chemotherapy which was not considered in our patient due to his poor performance status.

Prostatic LCNEC which is described only in case reports needs to be identified as it is associated with a higher stage, higher grade and worse prognosis[9]. The fact that subclinical DIC is rare in neuroendocrine carcinomas of solid organ tumors[12] makes our case unusual and intriguing.

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LEGENDS:

Figure 1A,B: Peripheral Blood Smear: Leucoerythroblastic Reaction [A (Romanowsky stain,40X): Blasts; B (Romanowsky stain,40X): Left shift, nucleated red blood cells]

Figure 2 Ai and Aii: BM Aspirate Smears are hypercellular exhibiting predominantly cohesive clusters and discrete malignant epithelial cells. [Ai:(Romanowsky stain,4X) and Aii: (Romanowsky stain,40X)]

Figure 3 A and B: BM biopsy sections show near complete replacement by sheets and cohesive clusters/groups of malignant epithelial cells separated by fibrous septa.(3A,H and E,10X). These tumour cells were large,polygonal with round nucleus, vesicular chromatin and prominent nucleolus with moderate amounts of vacuolated/clear cytoplasm (3B,H and E,40X)

Figure 4: BM reticulin fibrosis was increased. (Reticulin stain,10X)

Figure 5: Immunostains done on BM biopsy sections:-

5A: PSA(40X) immunostain was negative. 5B,C: Synaptophysin, Chromogranin A (40X) immunostains were strongly and diffusely positive in all the tumour cells. 5D: CK8/18 (40X) was also strongly and diffusely positive in all the tumour cells.

Figure 6A: MRI Pelvis:- T2 weighted axial image shows focal hypointense lesion involving the peripheral zone of Prostate (arrow)

Figure 6B: MRI Pelvis:- T2 weighted axial image shows pelvic lymphnodes (square box)

CONFLICT OF INTEREST: Authors declared no conflict of interest